Emerging Therapies for Serious Gram-Positive Bacterial Infections: A Focus on Linezolid

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Respiratory tract infections and skin and soft-tissue infections frequently are caused by gram-positive cocci, and treating these infections with standard antibiotics has recently become problematic. Many of the primary pathogens causing these infections are now resistant to current standard treatment regimens. In addition, the frequency of these infections is increasing, particularly among patients with complex medical conditions. Thus, new and effective antimicrobial agents are needed, and many are currently in various stages of development. Linezolid, the first approved oxazolidinone, has enhanced activity against gram-positive organisms. Recent results of 5 large, randomized, phase 3 trials evaluating linezolid for the treatment of community-acquired pneumonia, nosocomial pneumonia, and uncomplicated and complicated skin and soft-tissue infections are encouraging and indicate that linezolid is as effective as standard comparator agents as therapy for these infections. Thus, the recent availability of linezolid offers clinicians a promising new agent for the treatment of serious gram-positive bacterial infections.

The incidence of infections with resistant gram-positive cocci increased significantly during the 1990s. The risk of acquiring a serious gram-positive bacterial infection is influenced by numerous patient-related factors, including age, underlying disease, and immune status. Respiratory tract infections with Streptococcus pneumoniae and skin and soft-tissue infections with resistant Staphylococcus aureus have been particularly problematic. For more than 3 decades, S. pneumoniae infection was treated successfully with penicillin-based regimens; however, this pathogen has recently acquired resistance to many antimicrobial agents, including penicillin, cephalosporins, macrolides, and quinolones [1–3]. Similarly, staphylococci rapidly developed resistance to penicillin via penicillinase production, and >90% of S. aureus strains are now resistant to penicillin [4]. Thus, emphasis has been placed on developing new antimicrobial agents with enhanced activity against these increasingly resistant gram-positive cocci.

Clinical Need for New Therapies for Serious Gram-Positive Bacterial Infections

Antimicrobial resistance is one of the most significant sources of emerging and reemerging infectious diseases [5]. More specifically, the rise in antimicrobial resistance in gram-positive species has highlighted concerns regarding appropriate antibiotic use and the need for newer agents. The major gram-positive pathogen of community-acquired respiratory tract infections is S. pneumoniae, which is typically isolated from approximately one-third of patients with community-acquired pneumonia [6–8]. Other bacterial pathogens implicated in community-acquired pneumonia include atypical pathogens, such as Mycoplasma pneumoniae and Legionella species, and various other gram-positive and gram-negative organisms, such as S. aureus, Haemophilus influenzae, and Pseudomonas aeruginosa.

The incidence of penicillin-resistant S. pneumoniae isolates increased steadily in the United States throughout the 1990s. According to 1997 results from the SENTRY Antimicrobial Surveillance Program, the overall rate of penicillin resistance among respiratory tract isolates of S. pneumoniae in the United States was 43.8%; 16% of strains were highly resistant to penicillin [9]. Of particular concern, S. pneumoniae has also become increasingly resistant to cephalosporins, macrolides, tetracyclines, and trimethoprim-sulfamethoxazole [9–11]. There is significant geographic variability in resistance patterns, with a higher incidence of resistant strains in the southeastern United States than in other parts of the nation.

Although gram-negative organisms historically accounted for most cases of nosocomial pneumonia, the proportion of nosocomial infections due to gram-positive organisms has increased over the past 15 years [12–14]. The most important gram-positive pathogen of nosocomial respiratory tract infections is S. aureus. Methicillin resistance in S. aureus isolates has increased over the past 15 years. In the United States, rates of methicillin-resistant S. aureus (MRSA) vary by geographic region, with the highest proportions observed in the eastern part of the United States (southeastern region, 38.5%; northeastern region, 29.8% [as of April 1998]) [15]. The incidence of MRSA in teaching hospitals increased from 8% in 1986 to 40% in 1992 [16]. Currently, 50% of the isolates of S. aureus in our medical center are methicillin resistant. These increasing rates of MRSA...
Table 1. Antimicrobial activity against resistant gram-positive organisms.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Linezolid</th>
<th>Quinupristin/dalfopristin</th>
<th>Daptomycin</th>
<th>LY333328</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxacillin-resistant <em>Staphylococcus aureus</em></td>
<td>0.5±8</td>
<td>ND</td>
<td>ND</td>
<td>0.12±4</td>
</tr>
<tr>
<td>Penicillin-resistant <em>Streptococcus pneumoniae</em></td>
<td>0.06±4</td>
<td>0.12±4</td>
<td>ND</td>
<td>≤0.01±0.06</td>
</tr>
<tr>
<td>Methicillin-resistant <em>S. aureus</em></td>
<td>1.0±8.0</td>
<td>≤0.12±4</td>
<td>0.06±0.5</td>
<td>0.25±2</td>
</tr>
<tr>
<td>Vancomycin-resistant <em>Enterococcus</em> species</td>
<td>1±4</td>
<td>0.12-4^a</td>
<td>ND</td>
<td>≤0.12</td>
</tr>
<tr>
<td>Methicillin-resistant <em>Streptococcus agalactiae</em></td>
<td>2.0±4.0</td>
<td>≤0.12±8.0</td>
<td>0.13±2.0</td>
<td>≤0.12±1</td>
</tr>
</tbody>
</table>

NOTE. Data are from [38-43]. ND, no data available.

^a *Enterococcus faecium* only; not active against *Enterococcus faecalis*.

have prompted an increase in the empirical use of vancomycin for the treatment of nosocomial pneumonia. However, the recent emergence of *S. aureus* strains with reduced susceptibility to vancomycin in the United States and Japan is alarming and may limit the efficacy of this agent in the future [17-21].

In the common causative pathogens of skin and soft-tissue infections, antimicrobial resistance also has been observed. Major organisms causing skin and soft-tissue infections include streptococci (e.g., *Streptococcus pyogenes* and *Streptococcus agalactiae*) and *S. aureus*. According to the SENTRY Antimicrobial Surveillance Program, *S. aureus* accounted for 42.6% of clinical isolates from patients in the United States and Canada who had skin and soft-tissue infections in 1997 [22]. Other common gram-positive pathogens isolated include *Enterococcus* species (81%), β-hemolytic streptococci (6.3%), and coagulase-negative staphylococci (3.8%) [22]. Some *S. pyogenes* strains implicated in skin and soft-tissue infections produce toxins that can cause rapidly progressive myonecrosis. Although *S. pyogenes* remains susceptible to β-lactam agents, other streptococci have developed resistance to many of the β-lactam drugs as well as the macrolide antibiotics. MRSA is the causative organism identified in up to 22% of skin infections; in addition, common skin and soft-tissue pathogens are becoming increasingly less susceptible to macrolides [23]. Thus, new antimicrobial agents with enhanced activity against these increasingly resistant pathogens are needed.

**Emerging Therapies for Serious Gram-Positive Bacterial Infections**

The recent emergence of multidrug-resistant gram-positive pathogens underscores the need for new antimicrobial therapies. In 1998, a report by the Pharmaceutical Researchers and Manufacturers of America [24] indicated that 136 new agents were in development for the treatment or prevention of infectious diseases, including new glycopeptides (e.g., daptomycin and LY333328), ketolides (e.g., HMR3647), oxazolidinones (e.g., SCH27899), and oxazolidinones (e.g., linezolid). Since this report, clinical trials for SCH27899 have been discontinued because of insufficient clinical data supporting its efficacy and safety. In addition, quinupristin/dalfopristin, the first streptogramin agent, was approved in 1999 for the treatment of bloodstream infections and skin and skin-structure infections due to drug-resistant organisms [25].

**Linezolid.** Linezolid is the first member of a structurally unique class of antibiotics, the oxazolidinones [26]. These antimicrobial agents have a novel mechanism of action in that they inhibit bacterial protein synthesis by blocking formation of the initiation complex [27, 28]. Linezolid has demonstrated activity against gram-positive organisms resistant to other antimicrobial agents, including MRSA, penicillin-resistant *S. pneumoniae*, and vancomycin-resistant enterococci [29-35]. Although linezolid’s spectrum of activity is essentially limited to gram-positive bacteria, it does possess modest activity against *H. influenzae* and *Moraxella catarrhalis* [36]. Linezolid is bacteriostatic against most susceptible organisms; however, it exhibits bactericidal activity against some strains of pneumococci, *Bacteroides fragilis*, and *Clostridium perfringens* [37]. With twice-daily administration, linezolid blood levels exceed the MIC<sub>90</sub> for *S. aureus*, *Enterococcus* species, and *S. pneumoniae* for most of the dosing interval [36]. The MIC ranges of linezolid, quinupristin/dalfopristin, daptomycin, and LY333328 for resistant gram-positive organisms are compared in table 1.

Linezolid recently was approved by the US Food and Drug Administration for the treatment of adults with nosocomial pneumonia, infections due to vancomycin-resistant *Enterococcus faecium*, complicated and uncomplicated skin and skin-structure infections, and community-acquired pneumonia [44]. Because of its unique mechanism of action, linezolid lacks cross-resistance to other antimicrobial agents [37]. The absolute bioavailability following oral administration of linezolid approaches 100%, allowing for a convenient switch to oral therapy without dosage adjustment when clinically indicated [37, 38]. In addition, linezolid is generally well tolerated; the most common adverse effects are diarrhea, headache, and nausea [44, 45].

Linezolid’s efficacy and safety have been compared with those of comparator or placebo agents in phase 3 trials including >4000 patients (Pharmacia, unpublished data). Results from randomized phase 3 trials evaluating linezolid for treatment of respiratory infections and skin and skin-structure infections are discussed below.

**Linezolid as treatment of community-acquired pneumonia.** In a randomized, single-blind study that included >540 adult
outpatients with community-acquired pneumonia, linezolid (600 mg orally twice daily) was compared with cefpodoxime (200 mg orally twice daily) (table 2) [46]. Treatment continued for 7–14 days, with follow-up at 15–21 days after the end of therapy. Approximately 22% of patients had multilobar pneumonia, and ~9% had pleural effusion at baseline (Pharmacia, unpublished data). Of 201 clinically evaluable patients who received linezolid treatment, 180 (~90%) had clinical cure; similarly, 187 (~91%) of 206 patients who received cefpodoxime treatment had clinical cure \((P = .68)\). Among 49 microbiologically evaluable patients who received linezolid treatment, the microbiological success rate was 88% (43); among 47 microbiologically evaluable patients who received cefpodoxime treatment, the microbiological success rate was 89% (42) [46]. Rates of eradication of \(S.\ pneumoniae\), \(S.\ aureus\), and \(H.\ influenzae\) were 88.9% (24 of 27), 91.7% (11 of 12), and 83.3% (10 of 12), respectively, for patients treated with linezolid and 90.5% (19 of 21), 91.7% (11 of 12), and 86.7% (13 of 15), respectively, for those treated with cefpodoxime (Pharmacia, unpublished data).

The most common treatment-related adverse events were diarrhea, nausea, and headache; these events were generally mild to moderate in intensity and similar between treatment groups [46]. There were 2 deaths described in the linezolid treatment group, and none in the cefpodoxime treatment group. Although both deaths occurred early during the course of treatment, neither was considered treatment related (Pharmacia, unpublished data).

Another multinational, randomized, open-label trial evaluated linezolid as treatment of >700 patients with community-acquired pneumonia who required hospitalization (table 2) [47]. Patients received either linezolid (600 mg iv twice daily) or ceftriaxone (1 g iv twice daily), which was switched to oral linezolid (600 mg twice daily) or oral cefpodoxime (200 mg twice daily), respectively, at the investigator's discretion. Follow-up occurred at 15–21 days after the end of treatment. In both clinically evaluable treatment groups at baseline, ~15% of patients had pleural effusion, and ~34% of patients presented with multilobar pneumonia (Pharmacia, unpublished data). Among 272 clinically evaluable patients in the linezolid treatment group, the clinical cure rate was 91% (247); among 254 patients in the ceftriaxone/cefepoxide treatment group, the clinical cure rate was 89% (225) \((P = .4)\) [47]. Rates of eradication of \(S.\ pneumoniae\) and \(S.\ aureus\) for patients treated with linezolid were 89% (63 of 71) and 90% (18 of 20), respectively, with similar rates observed for patients treated with ceftriaxone/cefepoxide (90% [62 of 69] and 77% [13 of 17], respectively; \(P > .2\)) (Pharmacia, unpublished data). For a subset of 53 patients for whom blood cultures were positive for \(S.\ pneumoniae\), there was a clinical cure rate of 93% among the 30 patients who received linezolid treatment, compared with 70% among the 23 patients who received ceftriaxone/cefepoxide treatment \((P = .02)\) [48].

No demographic or baseline history information explains the fact that the clinical cure rate achieved with linezolid treatment was higher than that achieved with cephalosporin treatment for patients with \(S.\ pneumoniae\) community-acquired pneumonia and bacteremia. Diarrhea and nausea were the most common adverse events described in both treatment groups. Although there were slightly more deaths in the ceftriaxone/cefepoxide treatment group (19) than in the linezolid group (15), none of the deaths in either group were attributed to study medication, and most occurred during the posttreatment period (Pharmacia, unpublished data; [48]).

**Table 2.** Results of phase 3 trials of linezolid versus comparator agents as treatment of pneumonia: clinical efficacy for evaluable patients.

<table>
<thead>
<tr>
<th>Agent</th>
<th>No. of patients with clinical cure/total no. treated (%)</th>
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<tbody>
<tr>
<td></td>
<td>Outpatients with CAP</td>
</tr>
<tr>
<td><strong>Linezolid</strong></td>
<td>180/201 (90)</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>187/206 (91)</td>
</tr>
</tbody>
</table>

*NOTE.* Data are from [46–49]. CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia.

- a 600 mg twice daily; orally for outpatients with CAP and iv for inpatients with CAP and those with HAP
- b Cefpodoxime (200 mg orally twice daily).
- c Ceftriaxone (1 g iv twice daily); switched to cefpodoxime (200 mg orally twice daily) at investigator's discretion.
- d Vancomycin (1 g iv twice daily).

**Linezolid as treatment of hospital-acquired pneumonia.** A multinational, randomized, double-blind trial compared linezolid (600 mg twice daily; administered iv initially followed by a switch to oral therapy at the investigator’s discretion) with vancomycin (1 g iv twice daily) as treatment of 396 patients with hospital-acquired pneumonia (table 2) [49]. All patients also initially received aztreonam or aminoglycoside treatment, which could have been discontinued if gram-negative pathogens were not identified at baseline. Patients with only gram-negative pathogens at baseline were withdrawn from the study. Treatment was administered for 7–21 days, with follow-up at 15–21 days after the end of treatment. At baseline, approximately one-third of all clinically evaluable patients had pleural effusion, and multilobar pneumonia was observed in more than one-half of all clinically evaluable patients [49]. Of 107 clinically evaluable patients who received linezolid treatment, 66% (71) had clinical cure; of 91 clinically evaluable patients who received vancomycin treatment, 68% (62) had clinical cure \((P = .79)\). The microbiological success rate among the 53 microbiologically evaluable patients who received linezolid treatment was 68% (36) compared with 72% (28) among the 39 patients who received vancomycin treatment \((P = .69)\).

Rates of eradication of all \(S.\ aureus\) strains, the subset of MRSA isolates, and \(S.\ pneumoniae\) were 61% (25 of 41), 66.7% (14 of 21), and 100% (9 of 9), respectively, for the linezolid-treated patients; rates of eradication of all \(S.\ aureus\) strains, the subset of MRSA isolates, and \(S.\ pneumoniae\) were 65.2% (15 of 23), 70% (7 of 10), and 100% (9 of 9) \((P = .79)\), respectively.
for the vancomycin-treated patients (Pharmacia, unpublished data). Adverse event rates and safety evaluations were comparable for the 2 treatment groups [49]. Forty-nine of 198 vancomycin-treated patients (25%) and 36 of 198 linezolid-treated patients (18%) died. Deaths were attributed primarily to progression or complication of severe underlying comorbidities.

**Linezolid as treatment of uncomplicated skin and skin-structure infections.** In a multinational, randomized, double-blind study, linezolid (400 mg twice daily) was compared with clarithromycin (250 mg twice daily) as treatment of 332 adult patients with uncomplicated skin and skin-structure infections (table 3) [50]. Treatment continued for 7–14 days, with follow-up 7–21 days after the end of treatment. The most common diagnoses in both treatment groups at baseline were cellulitis, skin abscesses, and furuncle. Of 124 clinically evaluable patients who received linezolid treatment, 113 (91%) had clinical cure compared with 114 (93%) of 123 patients who received clarithromycin treatment [50]. For microbiologically evaluable patients, the microbiological success rate was 98% among linezolid-treated patients and 97% among clarithromycin-treated patients (P = .67) (Pharmacia, unpublished data). The rate of eradication of *S. aureus* was 97% (38 of 39) for the linezolid treatment and 96% (51 of 53) (P = .75) for the clarithromycin treatment group (Pharmacia, unpublished data). Adverse events were generally mild to moderate in intensity; nausea and diarrhea were the most common treatment-related adverse events in both treatment groups (Pharmacia, unpublished data). There were no deaths described in either treatment group during the study (Pharmacia, unpublished data).

**Linezolid as treatment of complicated skin and skin-structure infections.** A randomized, double-blind study compared linezolid (600 mg twice daily, administered iv initially, followed by a switch to oral therapy at the investigator’s discretion) with iv oxacillin (2 g 4 times daily) as treatment of 322 adult patients with uncomplicated skin and skin-structure infections (table 3) [50]. Treatment continued for 7–14 days, with follow-up 7–21 days after the end of treatment. Patients requiring therapeutic coverage for gram-negative organisms were allowed to receive aztreonam treatment. The most common baseline diagnoses in both treatment groups were cellulitis and skin abscesses [52]. Of 291 clinically evaluable patients who received linezolid treatment, 91% (264) had clinical cure; of 300 clinically evaluable patients who received oxacillin/dicloxacillin treatment, 86% (259) had clinical cure. Rates of eradication of *S. aureus*, *S. agalactiae*, and *S. pneumoniae* were 88% (73 of 83), 100% (6 of 6), and 69% (18 of 26), respectively, for linezolid-treated patients and 86% (72 of 84), 50% (3 of 6), and 75% (21 of 28), respectively, for oxacillin/dicloxacillin–treated patients [44]. Adverse events were generally mild to moderate in intensity, with nausea and headache as the most commonly described adverse events in both treatment groups. There were 3 deaths described in the linezolid treatment group and 1 in the oxacillin/dicloxacillin treatment group; none of the deaths were considered drug-related, with most occurring after treatment completion (Pharmacia, unpublished data).

### Table 3. Results of phase 3 trials of linezolid versus comparator agents as treatment of skin and soft-tissue infections (SSTIs): clinical efficacy for evaluable patients.

<table>
<thead>
<tr>
<th>Infection type, treatment regimen</th>
<th>No. of patients with clinical cure/total no. treated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated SSTIs</td>
<td></td>
</tr>
<tr>
<td>Linezolid (400 mg b.i.d.)</td>
<td>113/124 (91)</td>
</tr>
<tr>
<td>Clarithromycin (250 mg b.i.d.)</td>
<td>114/123 (93)</td>
</tr>
<tr>
<td>Complicated SSTIs</td>
<td></td>
</tr>
<tr>
<td>Linezolid (600 mg b.i.d.)</td>
<td>264/291 (91)</td>
</tr>
<tr>
<td>Oxacillin (2 g q.i.d.)</td>
<td></td>
</tr>
<tr>
<td>Dicloxacillin (500 mg q.i.d.)</td>
<td>259/300 (86)</td>
</tr>
</tbody>
</table>

NOTE: Data are from [50–52].

### Summary

One of the major shifts in the relationship of microorganisms and antibiotics has been the increased incidence of antimicrobial-resistant gram-positive pathogens. Treatment of serious gram-positive bacterial infections is complicated by this emergence of resistant pathogens and by increasingly complex patient populations who are susceptible to these pathogens. Researchers continue to develop new and effective antimicrobial agents. One recently approved agent, linezolid, is an oxazolidinone with substantial activity against both susceptible and resistant gram-positive organisms and is available in both iv and oral (tablet and oral suspension) formulations, allowing flexibility in dosing and convenience for patients. Furthermore, results of recent phase 3 trials demonstrate that linezolid is well tolerated and as effective as comparator agents. Thus, the availability of linezolid for the treatment of respiratory tract infections and skin and skin-structure infections due to gram-positive bacteria offers an effective new therapy for these often difficult-to-treat conditions.

### References


